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Abciximab in the Treatment of Acute Myocardial Infarction Eligible for Primary Percutaneous Transluminal Coronary Angioplasty

Results of the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) Pilot Study

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OBJECTIVES We sought to study the effect of early infusion of abciximab on coronary patency before primary angioplasty in patients with acute myocardial infarction.

BACKGROUND Glycoprotein IIb/IIIa antagonists have proved to be effective in reducing ischemic events associated with coronary angioplasty. The present study explores whether abciximab alone, without administration of thrombolytic therapy, may induce reperfusion in patients with acute myocardial infarction.

METHODS In the Glycoprotein Receptor Antagonist Patency Evaluation pilot study 60 patients with less than 6 h signs and symptoms of acute myocardial infarction eligible for primary angioplasty received in the emergency room a bolus of abciximab 250 μg/kg followed by a 12-h infusion of 10 μg/min. All patients were also treated with an oral dose of 160 mg aspirin and 5,000 IU of heparin intravenously. As soon as possible a diagnostic angiography was performed to evaluate the patency of the infarct-related artery.

RESULTS The median time between onset of symptoms and the administration of the abciximab bolus was 150 min (range 45 to 345), and the median time between abciximab bolus and first contrast injection in the infarct-related artery was 45 min (range 10 to 150). In 24 patients (40%, 95% confidence interval 28% to 52%) Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 was observed at a median time of 45 min (range 10 to 150) after abciximab bolus; TIMI flow grade 3 was observed in 11 patients (18%, 95% confidence interval 9% to 28%). There was no difference in percentage of TIMI flow grade 2 or 3 between patients who received abciximab within 2.5 h after onset of symptoms or thereafter.

CONCLUSIONS Abciximab therapy given in the emergency room in patients awaiting primary angioplasty is associated with full reperfusion (TIMI flow grade 3) in about 20% and with TIMI flow grade 2 or 3 in about 40% of the patients at a median time of 45 min. These figures are higher than those in primary angioplasty trials without such pretreatment. Randomized controlled trials of very early infusion of abciximab, either prehospital or in-hospital, in patients eligible for angioplasty are warranted. (J Am Coll Cardiol 1999;33:1528–32) © 1999 by the American College of Cardiology

Early reperfuion of the occluded coronary artery is the aim of treatment in patients with acute myocardial infarction. Either pharmacologic therapy (1–3) with thrombolytic drugs or mechanical treatment with primary coronary angioplasty (4–6) can be used. Thrombolytic therapy has the disadvantages of bleeding complications, thrombin generation and partial efficacy. The results of routine coronary angioplasty after thrombolysis are disappointing (7). Primary angioplasty can achieve patency in over 90% of the patients, but has logistic limitations including the inherent time delay, which may exceed 100 min even in angioplasty-dedicated centers. During this "door-to-balloon time" usually aspirin, nitroglycerin and sometimes low dose heparin are given, but specific reperfusion therapy is usually avoided,

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Abbreviations and Acronyms

GRAPE = Glycoprotein Receptor Antagonist Patency Evaluation
GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator in Occluded Arteries
TIMI = Thrombolysis in Myocardial Infarction

since its use in connection with angioplasty is associated with an increased complication rate. Recently, high dose bolus heparin has been shown to improve patency before primary angioplasty (8,9), but the safety and efficacy of high dose bolus heparin need confirmation.

Glycoprotein IIb/IIIa receptor antagonists given in patients undergoing coronary angioplasty have shown a beneficial effect in reducing ischemic events. Furthermore, patients with acute coronary syndromes treated with glycoprotein antagonists showed a better outcome compared with standard therapy (10–14). These studies showed that glycoprotein IIb/IIIa antagonists can safely be given intravenously, although they are associated with a higher bleeding risk (14).

At this moment there is limited information available about the effects of glycoprotein receptor antagonists on patency of the infarct-related artery in acute myocardial infarction. Recently, Gold et al. (15) showed a high infarct-related artery patency rate 10 min after a single dose of abciximab given intravenously in addition to aspirin and heparin. The drug was given in the catheterization laboratory without thrombolytic therapy.

The purpose of the present pilot study was to determine whether abciximab given to patients awaiting primary angioplasty for acute myocardial infarction would be adequate to establish coronary patency in the absence of thrombolytic therapy. We selected patients in the emergency room who were eligible for primary angioplasty and treated them during the delay period until the actual performance of the procedure.

METHODS

Patients of 80 years of age or less with signs and symptoms of a large acute transmural myocardial infarction with onset of symptoms within 6 h and a sum of ST-segment elevation of 10 mm or more were eligible for entry in this study. Patients with a contraindication to antiplatelet therapy, signs of active bleeding or inability to give informed consent were excluded. The patients included were recruited in five hospitals in The Netherlands and two in Sweden.

After the decision to perform primary angioplasty, all patients were treated with an oral dose of aspirin (160 mg) and heparin 5,000 IU intravenously in the emergency room. After oral informed consent they also received a bolus of abciximab of 250 μg/kg followed by 10 μg/min infusion. As soon as possible patients were transported to the catheterization laboratory where coronary angiography was performed. The end point in this study was patency of the infarct-related artery at first contrast injection.

Table 1. Baseline Characteristics of the Patients in the GRAPE Pilot Study

Number of patients (n)	60
Age (years, median, range)	63 (31 to 76)
Male (%)	70
Time from onset of symptoms to treatment (min, median, range)	150 (35 to 345)
Time from abciximab bolus to first contrast injection (min, median, range)	45 (10 to 150)

GRAPE = Glycoprotein Receptor Antagonist Patency Evaluation.

Patency of the infarct-related artery was scored according to the Thrombolysis in Myocardial Infarction (TIMI) flow grading scale (16) by two independent experienced investigators at the core lab (Cardialysis, Rotterdam, The Netherlands). Further treatment regimen was left at the discretion of the attending physician.

RESULTS

Between November 1996 and July 1997 60 patients were enrolled. The baseline characteristics of the patients are given in Table 1.

There was a relatively wide range in the time interval between the onset of symptoms and the bolus abciximab therapy. Also the time between abciximab bolus and first contrast injection in the infarct-related artery varied considerably and could take up to 150 min.

The culprit lesion was located in the right coronary artery in 22 patients, in the left anterior descending coronary artery in 29 patients and in the left circumflex artery in 6 patients. In one patient the left main artery was subtotally occluded, and in two patients the infarct-related vessel was a venous bypass graft. In 36 patients (60%) TIMI flow grade 0 and 1 at first contrast injection was seen. Thrombolysis in Myocardial Infarction flow grade 3 was seen in 11 patients (18%, 95% confidence interval 9% to 28%) and TIMI flow grade 2 or 3 was seen in 24 patients (40%, 95% confidence interval 28% to 52%).

There was no difference in percentage of TIMI flow grade 2 and 3 between patients who received abciximab within 2.5 h after onset of symptoms (n = 30) or thereafter (n = 30), as depicted in Figure 1. There was also no difference in percentage of TIMI flow grade 2 and 3 between patients who underwent angiography within 45 min after the initiation of the abciximab administration and those who did thereafter.

None of the 60 patients in the trial had major hemorrhage leading to the need for blood transfusion. There were no in-hospital strokes, and no patient died.

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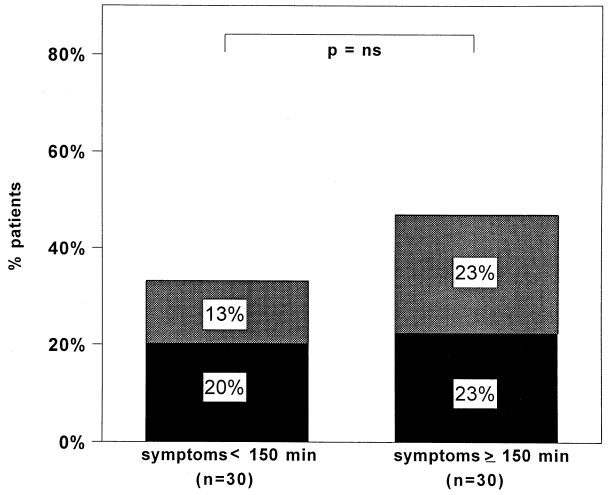

Figure 1. Relation between the time interval symptom onset–abciximab and the patency of the infarct-related artery at angiography. **Black bars:** Thrombolysis in Myocardial Infarction (TIMI) flow grade 2. **Gray bars:** TIMI flow grade 3.

DISCUSSION

Sofar, the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot trial is the largest to study the effect of abciximab on coronary patency in patients eligible for primary angioplasty for acute myocardial infarction. Furthermore, it is the largest study on emergency room initiation of glycoprotein receptor antagonist therapy in acute coronary syndromes.

In the GRAPE pilot study a positive effect of abciximab bolus given in the emergency room on early infarct-related artery patency became apparent with a TIMI flow grade 2 or 3 in 40% of patients at 45 min. Usually infarct-related artery patency (TIMI flow grade 2 or 3) in patients treated only with low dose heparin bolus and aspirin is poor and does not exceed 25% after 90 min (5,16,17). In our trial the patients received the abciximab bolus and started with the infusion therapy during the waiting time for the transfer from the emergency room to the catheterization laboratory.

Other observations. Our results are consistent with those of two other smaller patency studies on emergency room initiation of glycoprotein antagonists in patients with acute transmural myocardial infarction. In the reported, but not yet published Strategies for Patency Enhancement in the Emergency Department and TIMI-14A trials (18,19), abciximab bolus and infusion was initiated in the emergency room. Its effect on TIMI flow grade 3 evaluated at 60 and 90 min respectively is larger than in our trial, where the median time to angiography was only 45 min. Taken together, the three early abciximab trials, where TIMI flow grading was read in core labs, show significantly more TIMI flow grade 3 preangioplasty than the angioplasty arm of the Global Utilization of Streptokinase and Tissue Plasminogen Activator in Occluded Arteries (GUSTO)-IIb Angioplasty Substudy (17), the largest trial evaluating TIMI flow grades preangioplasty by core lab reading (chi-square test, Fig. 2). The same low percentage (<10%) of spontaneous TIMI flow grade 3 was found in the classic TIMI-1 (16) study and the control arms of the high dose heparin trials (8,9). Interestingly, in Figure 2 there seems to be a trend toward time dependency of abciximab in achieving TIMI flow grade 3.

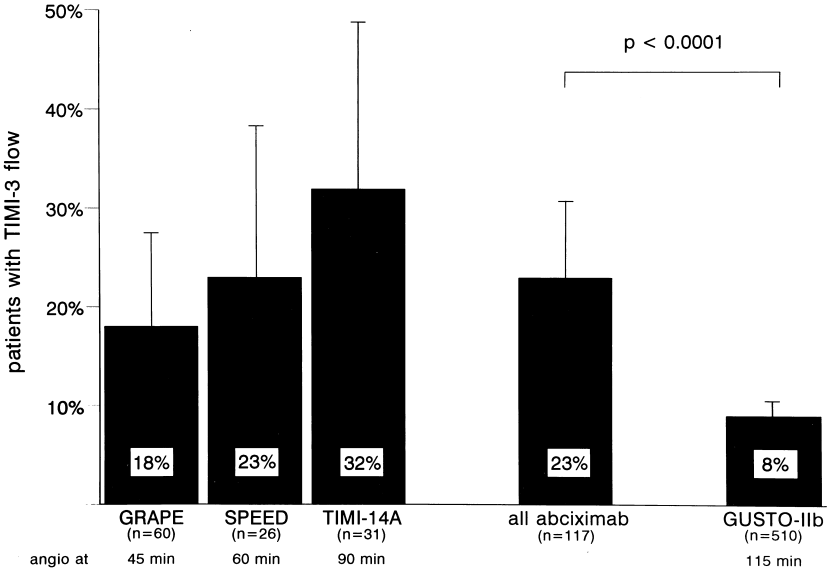

Figure 2. Preangioplasty Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 (with 95% confidence interval) in the reported emergency room initiated abciximab patency trials, each separately and together, compared with that preangioplasty in the angioplasty arm of the GUSTO-IIb Angioplasty Substudy (17). angio = angiography; GRAPE = Glycoprotein Receptor Antagonist Patency Evaluation; SPEED = Strategies for Patency Enhancement in the Emergency Department study.

Mechanism of reperfusion. Possibly, the combination of endogenous tissue plasminogen activator and the administered abciximab induces reperfusion. This may be explained by the anatomy of the occluding thrombus. Plaque rupture leads to a release of highly thrombogenic factors which activate platelets and the coagulation cascade. Platelet activation consists of presenting the glycoprotein IIb/IIIa receptor on the platelet surface at which fibrinogen can bind. The formation of fibrinogen dimers results in further aggregation (20,21). A fresh clot probably contains a large amount of platelets together with fibrin (white clot). As time passes by the clot will contain more and more fibrin, erythrocytes and white blood cells, and will become more stable (red clot). Thrombolytic agents are effective in dissolving fibrin and therefore they may achieve reperfusion. The remaining white clot and the ruptured vessel wall can give cause to early reocclusion. Antiplatelet therapy may positively influence this subtle balance of early reperfusion/reocclusion. This was already suggested by the aspirin results of the ISIS-2 trial (22). In our patient group thrombolytic therapy was not given, and the lytic effects we observed may have come from endogenous tissue plasminogen activator, whereas abciximab protects against further platelet aggregation and possibly reocclusion. We could not detect a temporal relationship between the age of the clot and the reperfusion efficacy of abciximab, as was found in the much smaller study of Gold (23). In that observation glycoprotein receptor antagonist treatment in the catheterization laboratory in 24 patients undergoing primary percutaneous transluminal coronary angioplasty was more effective in patients with a short time interval between symptom onset and the administration of abciximab. Interestingly the same phenomenon was observed with high dose bolus heparin in the HEAP pilot study (8). It should be noted that in the GRAPE pilot study patients were treated much earlier than in Gold's study and in about the same time window as the HEAP pilot trial. In the GRAPE pilot trial there was no relationship between the time from initiation of therapy and patency, which is usually seen in thrombolysis. In Gold's experimental and clinical study (15) it was suggested that abciximab induces reperfusion within 10 min. In our study vessels may have reoccluded in the meantime, which took an average of about 45 min. Given the very strong antiplatelet action of abciximab this is unlikely.

Further studies. Recently, a randomized placebo-controlled trial of abciximab given in the catheterization laboratory to 483 patients undergoing primary angioplasty for acute myocardial infarction was reported. The RAPPORT study showed a 36% reduction of death, reinfarction and revascularization ($p = 0.11$) in the patients receiving abciximab in the catheterization laboratory (24).

A combination of a reduced dose of thrombolytics with a glycoprotein IIb/IIIa receptor antagonist may improve the early patency rate further (18,19). The safety and efficacy of this strategy is currently being tested in the large GUSTO-IV and the TIMI-14 studies. Clearly, agents other than thrombolytics may induce reperfusion in some patients. Studies other than that of Gold (15) and our own indicate that nonthrombolytic reperfusion is possible; high dose heparin bolus may also have the same properties (8,9).

Study limitations. The most important limitation is the absence of a parallel control group. Furthermore, there is no angiographic follow-up after the moment of first contrast injection. The total number of patients is small with regard to safety and efficacy, and therefore further investigations are needed.

Conclusions. Thus, abciximab given in the emergency room to patients with acute myocardial infarction awaiting primary angioplasty is associated with TIMI flow grade 3 in about 20% and TIMI flow grade 2 or 3 in 40% of the cases at a median time of 45 min after initiation of therapy. This result is much better than in the primary angioplasty studies without abciximab pretreatment. However, the favorable angiographic outcome of our trial and two smaller observations should be tested in a randomized controlled trial, before this strategy can be implemented in the emergency room or the prehospital phase. Perhaps a combination of low dose thrombolysis and glycoprotein IIb/IIIa antagonist may improve these results further, which issue is currently under investigation.

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